

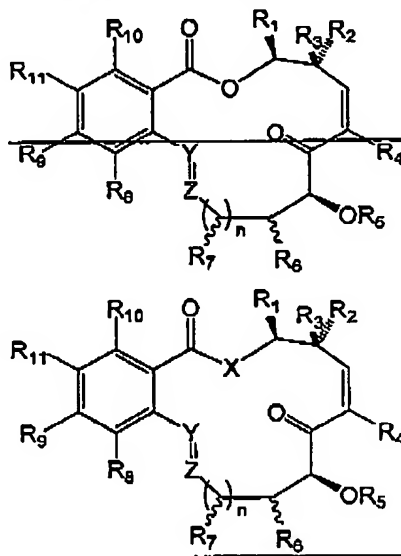
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NOV 29 2006

## AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. **(Currently Amended)** A pharmaceutical composition for systemic administration comprising a pharmaceutically suitable carrier or diluent and a compound having the structure:



or pharmaceutically acceptable derivative thereof;

wherein R<sub>1</sub> is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;

R<sub>2</sub> ~~and~~ is methyl;

R<sub>3</sub> ~~are each independently~~ is hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or

R<sub>4</sub> and R<sub>5</sub>, ~~when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or~~

R<sub>1</sub> and R<sub>3</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;

R<sub>4</sub> is hydrogen or halogen;

R<sub>5</sub> ~~is hydrogen, an oxygen protecting group or a prodrug~~ hydrogen or an oxygen protecting group;

R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

$R_8$  is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl,  $SR_{12}$ , or  $NR_{12}R_{13}$ ;

$R_9$  is hydrogen, halogen, hydroxyl, protected hydroxyl,  $OR_{12}$ ,  $SR_{12}$ ,  $NR_{12}R_{13}$ ,  $-X_1(CH_2)_pX_2-R_{14}$ , or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or  $-X_1(CH_2)_pX_2-R_{14}$ ;

wherein  $R_{12}$  and  $R_{13}$  are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or  $R_{12}$  and  $R_{13}$ , taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or  $-N(alkyl)$ , or wherein  $X_2-R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

$p$  is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is  $-(C=O)NHR_{15}$ ,  $-(C=O)OR_{15}$ , or  $-(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or  $R_{14}$  is  $-SO_2(R_{16})$ , wherein  $R_{16}$  is an aliphatic moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

$X$  is O, NH or  $CH_2$ ;

$Y$  is  $CHR_{17}$ ,  $O$ ,  $CR_{17}$  or  $NR_{17}$ ; and  $Z$  is  $CHR_{18}$ ,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or aliphatic, or  $R_{17}$  and  $R_{18}$  taken together

is -O-, -CH<sub>2</sub>- or -NR<sub>19</sub>-, wherein R<sub>19</sub> is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond;

wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine.

2. (Currently Amended) The composition of claim 1, wherein:

R<sub>1</sub> is hydrogen, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl;

R<sub>2</sub> and is methyl;

~~R<sub>3</sub> are each independently~~ is hydrogen, halogen, hydroxyl, protected hydroxyl, straight or branched lower alkyl, straight or branched lower heteroalkyl, or aryl,

wherein the alkyl, heteroalkyl, and aryl groups may optionally be substituted with one or more occurrences of halogen, hydroxyl or protected hydroxyl; or

~~R<sub>1</sub> and R<sub>2</sub>, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen; or~~

R<sub>1</sub> and R<sub>3</sub>, when taken together, may form a saturated or unsaturated cyclic ring of 3 to 8 carbon atoms, optionally substituted with one or more occurrences of halogen;

R<sub>4</sub> is hydrogen or halogen;

R<sub>5</sub> is hydrogen or a protecting group;

R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;

n is 0-2;

R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;

R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkyloxy, or lower alkyl optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;

R<sub>9</sub> is hydrogen, halogen, hydroxyl; protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or -X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>-R<sub>14</sub>;

wherein R<sub>12</sub> and R<sub>13</sub> are, independently for each occurrence, hydrogen, lower alkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or a protecting group, or R<sub>12</sub> and R<sub>13</sub>, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon

atoms and 1 to 3 nitrogen or oxygen atoms, and each of  $R_{12}$  and  $R_{13}$  are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen,

wherein  $X_1$  and  $X_2$  are each independently absent, or are oxygen, NH, or -N(alkyl), or wherein  $X_2$ - $R_{14}$  together are  $N_3$  or are a saturated or unsaturated heterocyclic moiety,

p is 2-10, and

$R_{14}$  is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is - $(C=O)NHR_{15}$  - $(C=O)OR_{15}$ , or - $(C=O)R_{15}$ , wherein each occurrence of  $R_{15}$  is independently hydrogen, alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl, or alkylheteroaryl, or  $R_{14}$  is - $SO_2(R_{16})$ , wherein  $R_{16}$  is an alkyl moiety, wherein one or more of  $R_{14}$ ,  $R_{15}$ , or  $R_{16}$  are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or

$R_8$  and  $R_9$  may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;

$R_{10}$  is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;

$R_{11}$  is hydrogen, hydroxyl or protected hydroxyl;

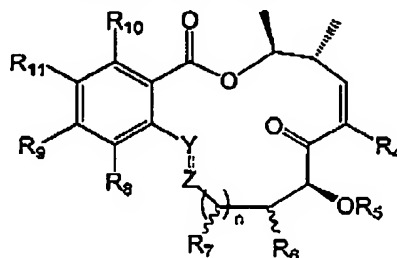
X is O:

Y is  $CHR_{17}$ ,  $CR_{17}$  or  $NR_{17}$ ; and Z is  $CHR_{18}$ ,  $C=O$ ,  $CR_{18}$  or  $NR_{18}$ , wherein each occurrence of  $R_{17}$  and  $R_{18}$  is independently hydrogen or lower alkyl, or  $R_{17}$  and  $R_{18}$  taken together is -O-, - $CH_2$ - or - $NR_{19}$ -, wherein  $R_{19}$  is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond.

3. (Previously Presented) The composition of claim 2, where n is 1.
4. (Original) The composition of claim 2, where  $R_4$  is halogen.
5. (Original) The composition of claim 2, where  $R_4$  is fluorine.
6. (Original) The composition of claim 2, where Y and Z together represent -CH=CH-

7. (Original) The composition of claim 2, where Y and Z together represent trans -CH=CH-.

8. (Previously Presented) The composition of claim 2, wherein R<sub>1</sub> and R<sub>2</sub> are each methyl and R<sub>3</sub> is hydrogen and the compound has the structure:



wherein R<sub>4</sub>-R<sub>11</sub>, n, Y and Z are as defined in claim 2.

9. (Previously Presented) The composition of claim 8, wherein n is 1.

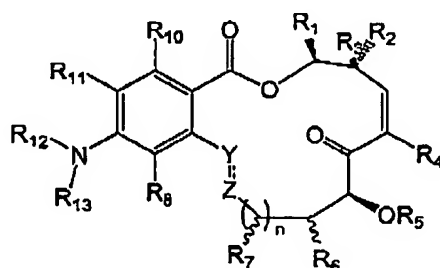
10. (Original) The composition of claim 8, wherein R<sub>4</sub> is halogen.

11. (Original) The composition of claim 8, wherein Y and Z together represent -CH=CH-.

12. (Previously Presented) The composition of claim 8, wherein n is 1, R<sub>4</sub> is halogen and Y and Z together represent -CH=CH-.

13. (Original) The composition of claim 11 or 12 wherein -CH=CH- is *trans*.

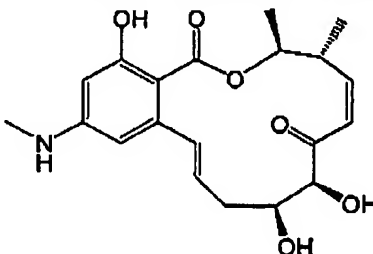
14. (Previously Presented) The composition of claim 2, wherein R<sub>9</sub> is NR<sub>12</sub>R<sub>13</sub> and the compound has the structure:



wherein  $R_1$ - $R_{13}$ ,  $n$ ,  $Y$  and  $Z$  are as defined in claim 2, or

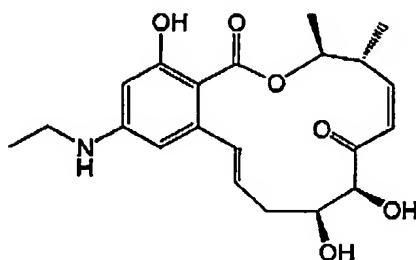
$R_{13}$  and  $R_8$  may, when taken together, form a cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydrogen, alkyloxy, amino, alkylamino, aminoalkyl, and halogen.

15. (Previously Presented) The composition of claim 14, wherein  $n$  is 1.
16. (Original) The composition of claim 14, wherein  $R_4$  is halogen.
17. (Original) The composition of claim 14, wherein  $Y$  and  $Z$  together represent  $-\text{CH}=\text{CH}-$ .
18. (Original) The composition of claim 14, wherein  $R_1$  and  $R_2$  are each methyl and  $R_3$  is hydrogen.
19. (Previously Presented) The composition of claim 14, wherein  $n$  is 1,  $R_1$  and  $R_2$  are each methyl,  $R_3$  is hydrogen,  $R_4$  is halogen, and  $Y$  and  $Z$  together represent  $-\text{CH}=\text{CH}-$ .
20. (Original) The composition of claim 17 or 19, wherein  $-\text{CH}=\text{CH}-$  is trans.
21. (Original) The composition of claim 1 wherein the compound has the structure:



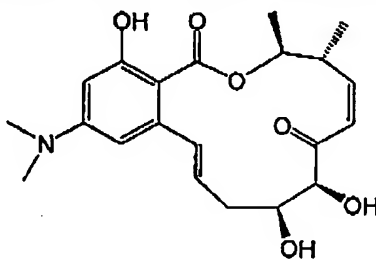
or pharmaceutically acceptable derivative thereof.

22. (Original) The composition of claim 1 wherein the compound has the structure:



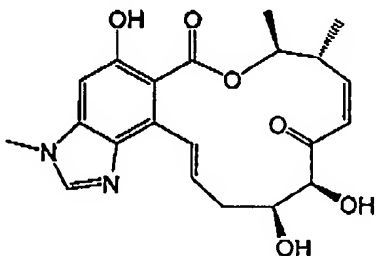
or pharmaceutically acceptable derivative thereof.

23. **(Original)** The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

24. **(Original)** The composition of claim 1 wherein the compound has the structure:

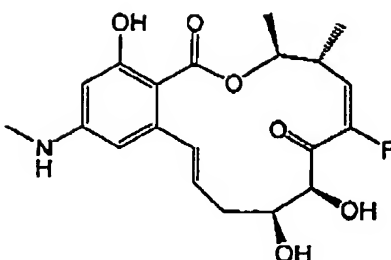


or pharmaceutically acceptable derivative thereof.

25. **(Canceled)**

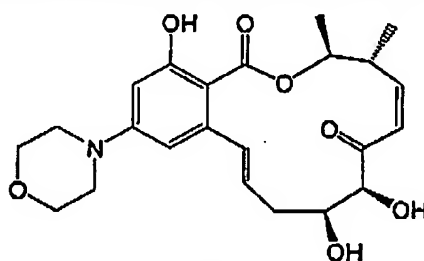
26. **(Canceled)**

27. **(Original)** The composition of claim 1 wherein the compound has the structure:



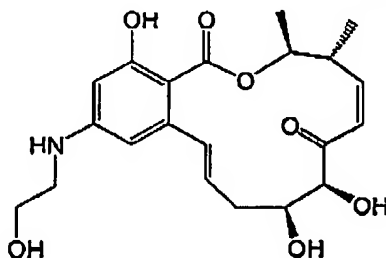
or pharmaceutically acceptable derivative thereof.

28. (Original) The composition of claim 1 wherein the compound has the structure:



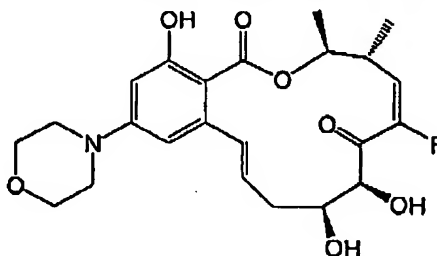
or pharmaceutically acceptable derivative thereof.

29. (Original) The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

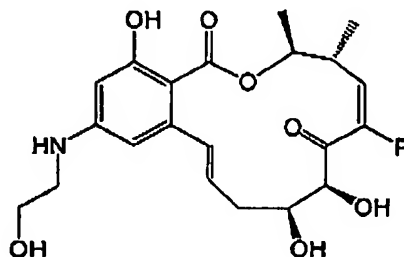
30. (Original) The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.



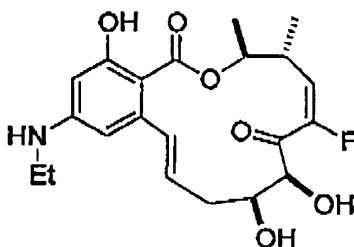
31. (Original) The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

32. (Canceled)

33. (Original) The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

34. (Canceled)

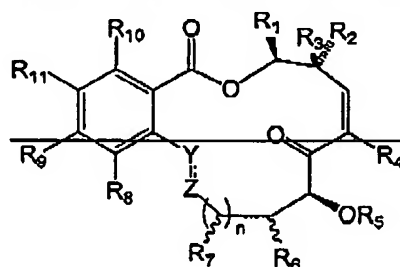
35. (Canceled)

36. (Original) The pharmaceutical composition of claim 1, wherein the composition is for oral administration.

37. (Canceled)

38. (Previously Presented) The pharmaceutical composition of claim 1, wherein the pro-inflammatory and/or immunologic cytokine is  $\text{TNF}\alpha$ , IL-1, IL-6, IL-8 or IL-2.

39. (Currently Amended) A method for treating rheumatoid arthritis, psoriasis, asthma, sepsis, inflammatory bowel disease, atopic dermatitis or Crohn's disease comprising the step of systemically administering to a subject in need thereof a pharmaceutically suitable carrier or diluent and a therapeutically effective amount of a compound having the structure: a therapeutically effective amount of a pharmaceutical composition of claim 1.



or pharmaceutically acceptable derivative thereof;

wherein ~~R<sub>1</sub> is hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl;~~

~~R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen, halogen, hydroxyl, protected hydroxyl, or an aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl moiety; or~~

~~R<sub>4</sub> and R<sub>5</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms; or~~

~~R<sub>4</sub> and R<sub>5</sub>, when taken together, may form a substituted or unsubstituted, saturated or unsaturated cyclic ring of 3 to 8 carbon atoms;~~

~~R<sub>4</sub> is hydrogen or halogen;~~

~~R<sub>5</sub> is hydrogen, an oxygen protecting group or a prodrug;~~

~~R<sub>6</sub> is hydrogen, hydroxyl, or protected hydroxyl;~~

~~n is 0-2;~~

~~R<sub>7</sub>, for each occurrence, is independently hydrogen, hydroxyl, or protected hydroxyl;~~

~~R<sub>8</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, alkoxy, or an aliphatic moiety optionally substituted with hydroxyl, protected hydroxyl, SR<sub>12</sub>, or NR<sub>12</sub>R<sub>13</sub>;~~

~~R<sub>9</sub> is hydrogen, halogen, hydroxyl, protected hydroxyl, OR<sub>12</sub>, SR<sub>12</sub>, NR<sub>12</sub>R<sub>13</sub>, X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>, R<sub>14</sub>, or is lower alkyl optionally substituted with hydroxyl, protected hydroxyl, halogen, amino, protected amino, or X<sub>1</sub>(CH<sub>2</sub>)<sub>p</sub>X<sub>2</sub>, R<sub>14</sub>;~~

~~wherein R<sub>12</sub> and R<sub>13</sub> are, independently for each occurrence, hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or a protecting group, or R<sub>12</sub>~~

~~and R<sub>12</sub>, taken together may form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms, and each of R<sub>12</sub> and R<sub>13</sub> are optionally further substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;~~

~~wherein X<sub>1</sub> and X<sub>2</sub> are each independently absent, or are oxygen, NH, or N(alkyl), or wherein X<sub>2</sub>-R<sub>14</sub> together are N<sub>3</sub> or are a saturated or unsaturated heterocyclic moiety,~~

~~p is 2-10, and~~

~~R<sub>14</sub> is hydrogen, or an aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or is (C=O)NHR<sub>15</sub>, (C=O)OR<sub>15</sub>, or (C=O)R<sub>15</sub>, wherein each occurrence of R<sub>15</sub> is independently hydrogen, aliphatic, heteroaliphatic, alicyclic, heteroalicyclic, aryl or heteroaryl; or R<sub>14</sub> is SO<sub>2</sub>(R<sub>16</sub>), wherein R<sub>16</sub> is an aliphatic moiety, wherein one or more of R<sub>14</sub>, R<sub>15</sub>, or R<sub>16</sub> are optionally substituted with one or more occurrences of hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen; or~~

~~R<sub>8</sub> and R<sub>9</sub> may, when taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen;~~

~~R<sub>10</sub> is hydrogen, hydroxyl, protected hydroxyl, amino, or protected amino;~~

~~R<sub>11</sub> is hydrogen, hydroxyl or protected hydroxyl;~~

~~Y is CHR<sub>17</sub>, CR<sub>17</sub> or NR<sub>17</sub>; and Z is CHR<sub>18</sub>, C=O, CR<sub>18</sub> or NR<sub>18</sub>, wherein each occurrence of R<sub>17</sub> and R<sub>18</sub> is independently hydrogen or aliphatic, or R<sub>17</sub> and R<sub>18</sub> taken together is O, CH<sub>2</sub> or NR<sub>19</sub>, wherein R<sub>19</sub> is hydrogen or lower alkyl, and Y and Z may be connected by a single or double bond;~~

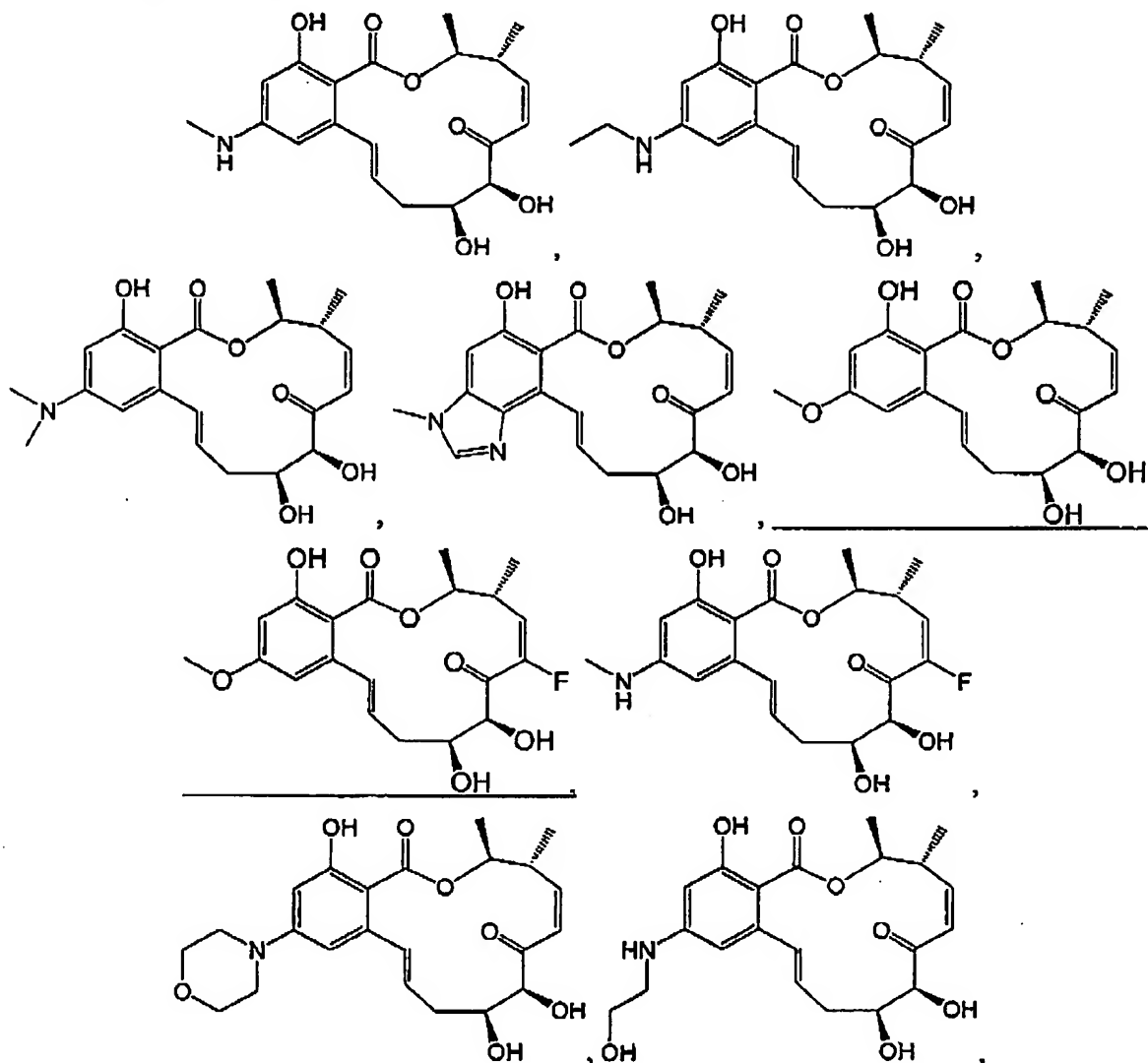
~~wherein the compound is present in an amount effective to inhibit production of a pro-inflammatory and/or immunologic cytokine.~~

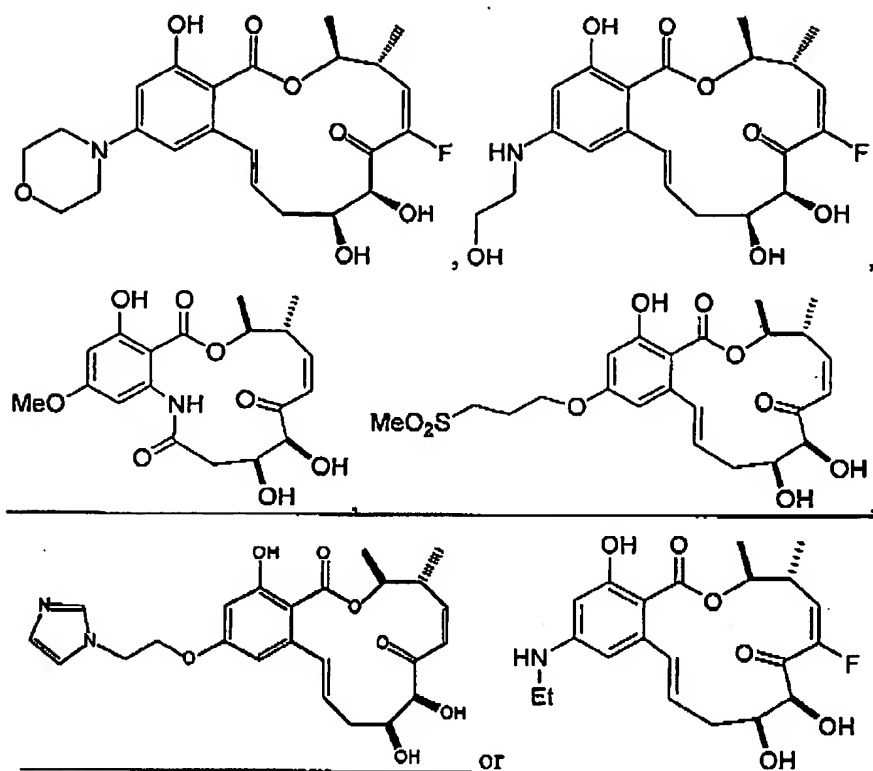
40. (Original) The method of claim 39, wherein the compound is administered orally.

41. (Canceled)

42. **(Previously Presented)** The method of claim 39, wherein the method is for treating psoriasis.

43. **(Currently Amended)** The method of claim 41, wherein the compound has any one of the following structures:





or pharmaceutically acceptable derivative thereof.

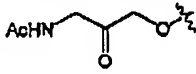
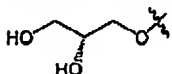
44. (Canceled)
45. (Previously Presented) The method of claim 39, wherein the pro-inflammatory and/or immunologic cytokine is  $\text{TNF}\alpha$ , IL-1, IL-6, IL-8 or IL-2.
46. (New) The composition of claim 2, where  $R_1$  is hydrogen or methyl.
47. (New) The composition of claim 2, where  $R_3$  is hydrogen or halogen.
48. (New) The composition of claim 2, where  $R_4$  is hydrogen.
49. (New) The composition of claim 2, where  $R_5$  is hydrogen.
50. (New) The composition of claim 2, where  $R_6$  is hydroxyl.

51. (New) The composition of claim 2, where  $R_7$  is hydrogen or hydroxyl.

52. (New) The composition of claim 2, where  $R_8$  is hydrogen or halogen.

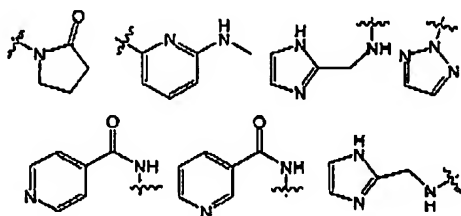
53. (New) The composition of claim 2, where  $R_9$  is hydroxyl, protected hydroxyl,  $-OR_{12}$ ,  $-NR_{12}R_{13}$  or  $-O(CH_2)_pX_2R_{14}$ , wherein  $R_{12}$ ,  $R_{13}$ ,  $R_{14}$  and  $X_2$  are as defined in claim 2.

54. (New) The composition of claim 53, where  $R_9$  is  $-OR_{12}$ , wherein  $R_{12}$  is methyl, ethyl,

propyl, isopropyl, butyl,  $-CH_2COOMe$ , Bn, PMB (MPM), 3, 4-ClBn, or  $R_9$  is  or 

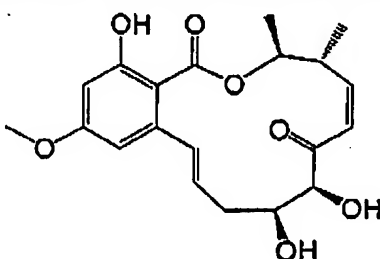
55. (New) The composition of claim 53, where  $R_9$  is  $-NR_{12}R_{13}$ , wherein  $R_{12}$  is methyl, ethyl, propyl, isopropyl, or butyl, optionally substituted with one or more occurrences of hydroxyl or protected hydroxyl, and  $R_{13}$  is hydrogen or lower alkyl, or  $NR_{12}R_{13}$  together represents a 5- or 6-membered heterocyclic moiety.

56. (New) The composition of claim 53, where  $R_9$  is  $-O(CH_2)_pX_2R_{14}$ , wherein  $X_2R_{14}$  together represent  $N_3$ ,  $NMe_2$ ,  $NHAc$ ,  $NHSO_2Me$ ,  $NHCONHMe$ ,  $NHCONHPh$ , morpholine, imidazole, aminopyridine, or any one of:



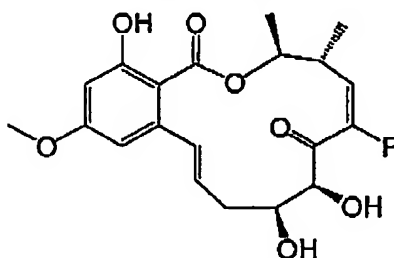
57. (New) The composition of claim 2, where  $R_8$  and  $R_9$ , taken together, form a saturated or unsaturated cyclic ring containing 1 to 4 carbon atoms and 1 to 3 nitrogen or oxygen atoms and is optionally substituted with hydroxyl, protected hydroxyl, alkyloxy, amino, protected amino, alkylamino, aminoalkyl, or halogen.

58. (New) The composition of claim 2, where  $R_{10}$  is hydroxyl.
59. (New) The composition of claim 2, where  $R_{11}$  is hydrogen.
60. (New) The composition of claim 2, where Y and Z together are cyclopropyl.
61. (New) The composition of claim 2, where Y and Z together are  $-NHC(=O)-$ .
62. (New) The composition of claim 1 wherein the compound has the structure:



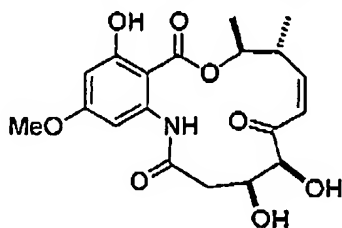
or pharmaceutically acceptable derivative thereof.

63. (New) The composition of claim 1 wherein the compound has the structure:



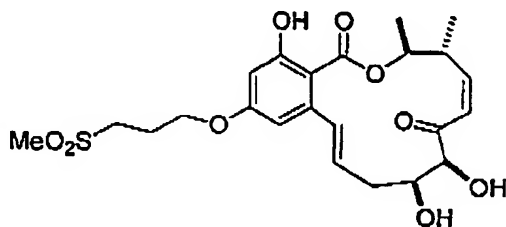
or pharmaceutically acceptable derivative thereof.

64. (New) The composition of claim 1 wherein the compound has the structure:



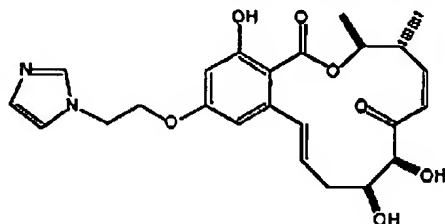
or pharmaceutically acceptable derivative thereof.

65. (New) The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.

66. (New) The composition of claim 1 wherein the compound has the structure:



or pharmaceutically acceptable derivative thereof.